Hematological side-effect profiles of individualized chemotherapy regimen for recurrent ovarian cancer

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The long-term results for patients with recurrent ovarian cancer (ROC) are poor. There is a need to optimize treatment strategies to improve outcome by avoiding ineffective regimens which are often associated with exacerbated side-effects. Individualized chemotherapy regimens guided by a chemosensitivity assay (ATP-tumor chemosensitivity assay) have already been used successfully to direct chemotherapy. Taking the results of this assay into account, application of drug combinations appears more advisable. Here we present a systematic evaluation of toxicities seen with individualized chemotherapy for ROC. A total of 62 patients who received 314 cycles of antineoplastic therapies were evaluated. Three single agents (topotecan, paclitaxel and gemcitabine) and five combinations (cisplatin/gemcitabine, carbopatin/gemcitabine, gemcitabine/treosulfan, mitoxantrone/paclitaxel and carboplatin/paclitaxel) were examined. With respect to myelotoxicity, most single agents except topotecan revealed favorable results in comparison to drug combinations. However, this observation lacks statistical significance. Generally, severe myelosuppression was rare. The highest incidence of leukopenia was seen in regimens with mitoxantrone/paclitaxel or gemcitabine/treosulfan, respectively. Thrombocytopenia accompanied most commonly a topotecan therapy. In the present study combination regimens tend to be more toxic than monotherapies. When response rates are comparable, empirically chosen treatment combination therapies should only be practiced in carefully planned clinical studies. ***Anti-Cancer Drugs*** **14:341–346 © 2003 Lippincott Williams & Wilkins.**

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Introduction

In contrast to the primary therapy, treatment of recurrent ovarian cancer (ROC) still varies widely. The benefit of secondary cytoreductive surgery and the drugs used for second-line chemotherapy is still a subject of controversy [1,2]. This is due to the fact that the entity 'ROC' covers a heterogeneous population. Therefore, a uniform therapy is unlikely to benefit all subpopulations equally. The entire group of ROC comprises both patients having experienced progress of the disease while being on, or within 6 months of, primary therapy and those presenting with recurrent tumor later than 6 months after administration of first-line treatment [3,4]. In patients presenting with late recurrence, secondary debulking surgery might be useful. Independently of a secondary surgical procedure, re-induction with platinum-based chemotherapy is considered the systemic treatment of choice in most of these cases. In patients relapsing within an interval of only 6 months after primary treatment, secondary surgery should be reserved for those suffering from medical problems such as bowel or ureter obstruction. In most of these cases, platinum-based chemotherapy has to be considered ineffective. The standard second-line therapy for patients with early recurrence who did not receive taxanes as part of their first-line treatment continues to be paclitaxel [5]. In a study conducted by the National Cancer Institute on 1000 patients with various prior therapies, a remission rate averaging *22%* was determined [6]. In addition to established substances, such as treosulfan and etoposide, more recent therapeutic regimens favor administration of topotecan, gemcitabine or liposomal doxorubicin, respectively. These latter novel agents represent therapeutic alternatives for platinum-refractory ROC; in particular, for those being pretreated with taxanes [7–9]. The particular therapy administered individually depends on the patient's general condition, and both the activity and toxicity [10]. However, the vast majority of patients with ROC must be considered incurable, regardless of the response duration after primary treatment.

Until the present, the planning of anti-neoplastic chemotherapy has been based exclusively on empirical considerations. Due to the non-satisfying long-term

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results of chemotherapy in ROC, time lost through ineffective regimens, exacerbated side-effects and unnecessary costs should be avoided. In particular, the concept of individualized chemotherapy offers the opportunity of a highly specific treatment with regard to both efficacy and toxicity for patients with platinum-refractory disease. To improve efficiency, the existence of a reliable predictive method to assess individual chemosensitivity is therefore highly desirable [11]. In spite of the significant progress in drug development made during the last decade, individual response to cytostatic treatment remains difficult to predict.

Many efforts have been made to develop test systems capable of accurately predicting the individual chemotherapy sensitivity of different patients, thus allowing for individualized therapy [12,13]. Recent non-clonogenic assays might be able to overcome technical limitations of older methods like the human clonogenic assays. The low evaluability rates, high number of tumor cells required or inadequate test duration should be eliminated. Currently, the most sensitive and best-validated method to assess the *ex vivo* chemosensitivity of native tumor cells derived from solid tumors is the ATP-tumor chemosensitivity assay (ATP-TCA). This assay provides a robust and reproducible methodology with high correlations between test results and clinical tumor response in both breast and ovarian cancer [14]. The ATP-TCA has already been used to successfully direct chemotherapy for patients with ROC [15]. In particular, favorable results were obtained in those patients suffering from platinum-refractory disease. Compared to empirical therapies, the assay-directed chemotherapy was capable of both dramatically increasing the number of clinically complete responses, and prolonging progression-free and overall survival by 2-fold. Consequently, the use of the ATP-TCA in ROC is now under clinical phase III evaluation. Apart from specific clinical trials, we routinely use the assay to guide chemotherapy in extensively pretreated patients with ROC. It is our experience from different clinical trials that the ATP-TCA favors the use of drug combinations rather than single agents. Combination regimens may be associated with an increased incidence of clinically relevant adverse effects. In particular, myelosuppression, which accounts for the majority of acute toxicities, may interfere markedly with the clinical utilization of the regimens. This retrospective study was undertaken to evaluate the hematological toxicity associated with ATP-TCA-directed salvage therapy in patients with ROC.

Materials and methods

A total of 62 tumor specimens from patients with ROC were tested for various single agents and drug combinations using the ATP-TCA in our institution between February 1996 and May 1999. Of the samples analyzed, 36 were ascites aspirates and 26 were solid tumor specimens. The samples were obtained either during secondary debulking surgery, or by paracentesis of the abdominal or pleural cavity due to significant production of malignant effusion. The median age of patients at the time of specimen collection was 61 years (range 39–79 years). ATP-TCA methodology was performed as previously described in detail [16].

Therapy was performed with the regimens exhibiting the best *ex vivo* activity providing an acceptable degree of anticipated side-effects (Tables 1 and 2).

Hematological toxicity pattern was routinely recorded for each therapy course according to the common WHO toxicity scale. In order to distinguish more accurately between therapy incompatibilities in this study, the use of various supportive drugs was also investigated. This comprises the use of several colony stimulating factors. In addition, side-effects actuated by blood transfusions and amifostine were also investigated.

Results

A total of 109 courses of single-agent therapy and 205 courses of polychemotherapy were evaluable for myelotoxicity. The degree of hematologic toxicity is shown in Table 3. There was a trend concerning myelotoxicity favoring most single agents except topotecan versus drug combinations. The highest incidence of anemia was seen with carboplatin/paclitaxel (grade 3–4: 16.6%) followed by topotecan (grade 3–4: 9.1%). Leukopenia was also most common in combination regimens with the highest incidence observed in regimens with novantrone/paclitaxel (grade 3–4: 12.8%) and gemcitabine/treosulfan (grade 3–4: 11.9%). Thrombocytopenia was most common with topotecan (grade 3–4: 12.2%). The consumption of supportive medication under all chemotherapy regimens investigated confirms the trend of a generally higher myelotoxicity in combination regimens (Table 4). The requirement for granulocyte colony stimulating

Table 1 Characteristics of monotherapies for ROC selected by ATP-TCA

Cytostatic regime	Dosage (mg/m^2)	Administration interval	Accompanying medication
Gemcitabine (45 cycles)	1000	day 1, 8, 16, q4w	5-HT$_3$ antagonists
Paclitaxel (31 cycles)	175	day 1, q3w	dexamethasone 8 mg i.v., clemastin i.v., ranitidin i.v., ondasetron 8 mg i.v.
Topotecan (33 cycles)	1.25	day 1–5, q3w	dexamethasone 8 mg i.v., ondasetron 8 mg i.v.

Table 2 Characteristics of drug combinations for ROC selected by ATP-TCA

Cytostatic regime	Dosage	Administration interval	Accompanying medication
Cisplatin/gemcitabine (30 cycles)	DDP 75 mg/m^2/dFdC 1250 mg/m^2	DDP day 1/dFdC 1 + 8, repeat day 21	dexamethasone 8 mg i.v., ondasetron 8 mg i.v.
Carboplatin/gemcitabine (63 cycles)	CBDCA AUC 5/dFdC 1250 mg/m^2	CBDCA day 1/dFdC 1 + 8, repeat day 21	dexamethasone 8 mg i.v., ondasetron 8 mg i.v.
Gemcitabine/treosulfan (59cycles)	TREO 5000 mg/m^2/dFdC 1250 mg/m^2	TREO day 1/dFdC 1 + 8, repeat day 21	dexamethasone 8 mg i.v., ondasetron 8 mg i.v
Mitoxantrone/paclitaxel (47 cycles)	MX 6 mg/m^2/PTX 100 mg/m^2	MX day 1/PTX 1 + 8, repeat day 15	dexamethasone 8 mg i.v., clemastin 2 mg i.v., ranitidin 50 mg i.v., ondasetron 8 mg i.v.
Carboplatin/paclitaxel (6 cycles)	CBDCA AUC 5/PTX 175 mg/m^2	repeat day 21	dexamethasone 8 mg i.v., clemastin 2 mg, ranitidin 50 mg, ondansetron 8 mg

Table 3 Review of the therapy regime used and the side-effects noted (WHO grade; percentage distribution)

Drugs	Anemia		Leukopenia		Thrombopenia	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Gemcitabine	25.6	0	44.4	4.4	24.4	6.7
Paclitaxel	67.7	6.5	61.3	0	41.9	0
Topotecan	78.8	9.1	78.8	3.0	66.7	12.2
Carboplatin/gemcitabine	76.2	4.8	71.4	3.2	41.3	1.6
Cisplatin/gemcitabine	66.7	6.7	66.7	0	43.3	0
Gemcitabine/treosulfan	84.8	5.1	72.9	11.9	28.8	8.5
Mitoxantrone/paclitaxel	80.9	6.4	86.6	12.8	29.8	8.5
Carboplatin/paclitaxel	100	16.6	100	0	33.4	0

Table 4 Consumption (%) of supporting drugs under the relevant chemotherapy regimes

Therapy regime	Erythropoietin	G-CSF	Amifostin	Erythrocyte concentrates
Gemcitabine (45 cycles)	0	42.2	6.7	0
Paclitaxel (31 cycles)	32.3	51.6	0	38.7
Topotecan (33 cycles)	24.2	30.3	57.6	18.8
Cisplatin/gemcitabine (30 cycles)	39.7	68.3	7.9	25.4
Carboplatin/gemcitabine (63 cycles)	23.3	70.0	0.0	13.3
Gemcitabine/treosulfan (59 cycles)	16.9	69.5	5.1	16.9
Mitoxantrone/paclitaxel (47 cycles)	31.9	78.7	0	34.0
Carboplatin/paclitaxel (6 cycles)	16.7	83.4	0.0	0.0

factor (G-CSF) was much lower in all single-agent regimens as compared to combination therapies. The need for erythropoietin and blood transfusions was highest in both paclitaxel-based combinations and paclitaxel alone. The frequent usage of amifostin with topotecan reflects the high incidence of thrombocytopenia with this substance.

Discussion

All the measures described for the treatment of ROC have one factor in common: their success is not predictable in individual cases. All the therapy options are to some extent subject of independent morbidity or even mortality, and also of side-effects, which in turn are of high impact considering an overall devastating situation. The patients' quality of life for their remaining time to progression or even death is decreased or seriously impaired by the therapeutic effort—in the worst cases possibly even without any objectifiable benefit [17,18]. However, the cytostatics or cytostatic regimes available exhibit various toxicity profiles, which are compared below.

Monotherapies

Gemcitabine

There are only few data available concerning the side-effect pattern of gemcitabine [19–21]. Here, in contrast to other cytostatics, a definitely favorable side-effect profile is described [22]. As expected in our patient collective, monotherapy with gemcitabine proved to be

the one with the lowest side-effect profile. Higher grades of anemia did not occur. In our collective, the hematological side-effects of a monotherapy with gemcitabine and paclitaxel are comparable, although the use of supporting measures was substantially higher in the latter regimen. Consequently, gemcitabine exhibited a more favorable side-effect profile, both in comparison to other monotherapies and in comparison to the combination therapies.

Paclitaxel

With respect to the hematological side-effects, leukopenia is the commonest and dose-limiting factor. In our cohort, grade 1 leukopenia occurred in 35.5% of the cycles, grade 2 in 25.8%. Higher grades of leukopenia or thrombopenia were not noted. Anemia grade ≥ 3 was present in 6.5% of cases. Consequently, the therapy with paclitaxel is more hematotoxic than gemcitabine, but slightly less so than that with topotecan [23].

Topotecan

Even at the dose-finding stage of topotecan, the necessity of prophylactic administration of G-CSF after the first cycle quickly became evident, by avoiding a reduction in the dose due to severe neutropenia [24]. Myelosupression is known to be the major toxicity from administration of topotecan. A phase II study [25] of i.v. topotecan as a 5-day infusion at dose levels of 1.5, 1.25 and 1.0 mg/m^2 showed an increased incidence of thrombocytopenia. Grade 4 thrombocytopenia was noted with 9% of all courses and for 23% of the patients. Anemia grade 3 or 4 was observed in 15% of the courses and for 37% of the patients. Those data are not comparable with the results of our study, because here in 57.6% of the cases a primary prophylactic dosage of amifostin was given to prevent higher-grade thrombo- and leukopenia. Thus our collective showed leukopenia grade ≥ 3 only in 3.0% of the cases. Thrombopenia grade ≥ 3 was noted in 12.2% of cases, anemia grade ≥ 3 in 9.1% of cases.

Combination therapies

Carboplatin/gemcitabine and cisplatin/gemcitabine

Two studies evaluated the combination of cisplatin plus gemcitabine [26,27] in relapsed ovarian cancer. The first study delivered cisplatin 30 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1, 8, 15 every 28 days. Myelosuppression was the major adverse effect and prompted a change in the regimen to cisplatin 30 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1, 8 every 21 days. In the second study cisplatin 40 mg/m^2 plus gemcitabine 1250 mg/m^2 were given i.v. on days 1, 8 every 21 days; 33% experienced grade 3–4 neutropenia and 20% grade 3–4 thrombocytopenia. Studies directly comparing the carboplatin/gemcitabine and cisplatin/gemcitabine doublets have not been published so far. In our investigation there were no differences between both combination regimens with respect to hematological side-effects (leukopenia grade ≥ 3: 0 versus 3.2%; thrombopenia grade ≥ 3: 0 versus 1.6%). Also in respect to anemia there were only marginal variations (anemia grade ≥ 2: 13.3 versus 15.8%, grade ≥ 3: 6.7 versus 4.8%).

Gemcitabine/treosulfan

The combination therapy investigated in this study consisting of treosulfan and gemcitabine has remained largely untested to date for the treatment of ROC. Favorable response rates for the therapy of heavily pretreated patients with breast and ovarian cancer were found in *ex vivo* studies employing ATP-TCA [28], indicating that the use of a combination for patients with ROC may be helpful.

Examination of the hematological side-effects revealed a moderate spectrum of higher-grade leukopenia (grade ≥ 3: 11.9%) and anemia (grade ≥ 3: 5.1%). Consequently, a pattern comparable to the combination of mitoxantrone/paclitaxel and to the monotherapy with topotecan was observed. In contrast to combinations of carboplatin/gemcitabine and cisplatin/gemcitabine, a decline of leukopenia and anemia were noted. With respect to therapy-related thrombopenia, treosulfan/gemcitabine was the only combination for which a grade 4 side-effect occurred. Similar data were obtained by Meden *et al.* [29] in a study conducted in 1997 on the use of orally administered treosulfan.

Mitoxantrone/paclitaxel

Nicoletto *et al.* [30] provided data of 82 patients who had been treated with this therapy regime. The response rates were good and the toxicity was comparable with that of paclitaxel monotherapy. In contrast to this study, the combination therapy revealed a increased side-effect rate in our patients group with respect to therapy-related leukopenia (grade ≥ 3: 0 versus 12.8%). The rate of grade ≥ 3 thrombopenia at 8.5% was likewise the highest of all the combination therapies. In our collective this is therefore considered the most hematotoxic combination.

As already stated, the combination therapies show a considerably higher toxicity in comparison to the monotherapies. This is also reflected in the consumption of supporting therapeutics. To prevent severe hematological side-effects, in 68.3% (cisplatin/gemcitabine) and 83.4% (carboplatin/paclitaxel) out of all cases, G-CSF was additionally administered. The consumption of erythropoietin and blood products was higher with the combination therapies. Corresponding doses were, for example, administered together with cisplatin/gemcitabine in 39.7 and 25.4% of the cycles. In 31.9% of cases erythropoietin was likewise given frequently during the treatment with mitoxantrone/paclitaxel. Under the gemcitabine/treosulfan therapy it was made use of in only

16.9% of cases. Therefore, if one compares the additional use of hematopoietic growth factors under chemotherapy, the carboplatin/paclitaxel combination shows the highest consumption. Overall these results reflect not only the trend towards more severe hematological side-effects for the combination therapies in comparison to the monotherapies, but also the differences between the various investigated combination therapies.

The observed side-effects under therapy with topotecan are largely hematotoxic in nature and the risk of thrombocytopenia, in particular, appears to be more pronounced. As a result, amifostin was used more frequently than with all the other investigated therapy regimes. The primary prophylactic use of amifostin also explains the lower incidence of thrombo- and leukopenia of our patient collective as compared to earlier studies. Gemcitabine therapy was employed only in individual cases. The use of erythropoietin accompanying topotecan therapy is also frequent at 24.2%, as is the consumption of erythrocyte concentrates (18.5% of all the cycles). These findings were exceeded by therapies with paclitaxel (erythropoietin 32.3%, erythrocyte concentrates 38.7%). The results correlate with the variations in therapy-related anemia for both schemes. Amifostin supplement was required to follow a gemcitabine monotherapy only in individual cases (6.7%). The administration of erythropoietin or banked blood was not necessary. When the three monotherapies are compared with respect to the requirement for G-CSF, the highest level was noted for paclitaxel (51.6%), followed by gemcitabine (42.2%). The lowest consumption of G-CSF, at 30.3%, was recorded for the topotecan therapy. One should, however, note that here amifostin was used for cell protection in 57.6% of the cycles, which is bound to have led also to a protective action for leukopoiesis. The results obtained correlate with the data described in the previous section on the hematological spectrum of side-effect spectrum. The necessity of employing certain supporting therapies can certainly affect the patient's quality of life substantially [17]. The amifostin therapy, for example, has a major adverse effect on individual well being, due to its considerable emetogenic potential.

Conclusion

The prognosis for platinum-refractory ROC, in particular, is extremely poor. In view of this, alongside the effectiveness of the therapy, the question of the relationship between cost, risk and stress must always be raised. With regard to therapy effectiveness, all the empirical regimes have produced disappointing results. Only a few substances show a cumulative response rate higher than 20%. In the present study, it could be confirmed that the combination therapies tend to be slightly more toxic than the monotherapies. When the response rates are comparable with empirically chosen treatment combination therapies should therefore only be practiced in carefully planned clinical studies. The use of preclinical test systems not only permits determination of the individual cytostatic sensitivity, but consequently the response rate of a therapy. It is also capable of providing at least partial answers to the questions of individual acceptability, practicality and stress of a therapy.

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